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Medical quality radiation resistant plasticized poly(vinyl chloride)

Summary — The effect of modification of plasticizer and stabilizer systems on the radiation resistance of flexible PVC compositions for medical applications was studied. Samples were irradiated in a linear accelerator LAE 13/9 of electrons beam with dose of 25 kGy. Biological-chemical and mechanical-physical property data were measured for irradiated and additionally ageing plasticized PVC compositions of modified formulations and compared with those of standard medical grade compositions. Post-irradiated stability of flexible PVC meeting the Pharmacopoeia requirements has been achieved.
Key words: plasticized PVC, medical materials radiation sterilization, radiation resistance, costabilizers, chemical and biological properties.

EFFECT OF IRRADIATION ON PVC COMPOSITIONS

Plasticized PVC is widely used to the manufacture of disposable medical devices, which should be sterile. The most commonly used sterilization methods include heat treatment, the use of chemical sterilants (*e.g.* ethylene oxide) or the exposure to ionizing radiation. Each of these methods has disadvantages that limit its use. The method using ethylene oxide is a cumbersome, time-consuming and expensive one and moreover ethylene oxide is toxic and cancerogenic medium. Thus when ethylene oxide as chemical sterilant is used, care must be taken to avoid gas residues in the devices and packages.

Recently the medical industry has begun to shift the sterilization technique of disposable medical devices from ethylene oxide to ionising radiation since it is an excellent and more efficient biologically, less expensive and less time-consuming method [l—3].

However, when exposed to ionizing radiation (*e.g.* gamma rays or electron beams) PVC materials undergo undesirable changes in physical, chemical and biological properties [4—8].

An excited molecule of PVC forms free radicals, which are responsible for several types of PVC transformations such as discoloration, cross-linking, chainscission and oxidation. A distinct discoloration of PVC composition occurs at a typical sterilization dose of 25 kGy, the material tends to darken or to turn yellow. During irradiation of PVC, conjugated double bonds are formed and hydrogen chloride in significant quantities is evoluted. The polyene structure is responsible for discoloration of PVC compositions. Oxygen also causes the formation of peroxide, carbonyl and hydroxyl groups. This is an autocatalytic process and it continues during the storage time of irradiated compositions [9—11].

A number of research studies have been made to improve radiation resistance of PVC compositions [12—16]. The key idea of all of them is to produce a protective effect by using compounds (*e.g.* organotin mercaptoacid esters and different types of aromatic compounds), which act as an energy transfer agent with no change of polymer properties. Unfortunately, most of them are toxic and cannot be used for medical formulations.

The effects of basic components and various additives on radiation stability of plasticized PVC compositions were permanently studied and discussed. Unfortunately, the result has not been univocally established.

According to the study of Hutzler et al. the mixture of plasticizers: di-2-ethylhexyl phthalate (DEHP) and epoxidised soybean oil (ESO), commonly used in medical compositions, is effective in stabilizing the radiolytic abstraction of HCl from PVC [17]. Both plasticizers imparted good colour stability and overall properties to the products.

In other opinion, the aliphatic plasticizers exhibit better performance than aromatic ones [12, 18]. The application of alkyl ester of adipic acid, mainly di(2-ethylhexyl)adipate (DOA), as plasticizer in PVC compositions improves the resistance of these products to irradiation. The PVC plasticized with DOA exhibits biological and chemical properties according to the European Pharmacopoeia [18].

Heat stabilizers can have a major effect on the performance of radiation stable PVC. Traditionally used in

medical formulation Ca/Zn stabilizing system alone is not powerful enough to provide irradiation stability of PVC. It was found that addition of radiation stabilizers (the type is not given) to the above Ca/Zn system shows remarkable improvement in the discoloration of the PVC during irradiation [19]. It can be due to the ability of the stabilizer to replace the labile chlorine with an ester group. Thus, in such a composition, the radiation stabilizer improves initial colour and radiation stability of PVC.

The present work also concerns the improvement of radiation resistance of plasticized PVC *via* modification of the composition formulation that allows to prepare the materials that are meeting the fundamental requirements for medical applications and retaining the high colour stability at sterilizing dose of 25 kGy.

EXPERIMENTAL

Materials

PVC — Polanvil S-70 SM, medical grade; $K = 70$ (Anwil SA, Włocławek, Poland).

Plasticizers: di-2-ethylhexyl phthalate (DEHP) — Vestinol AH (Hüls), tris-2-ethylhexyl trimellitate (TOTM) (Ciba-Geigy).

Stabilizers: Ca/Zn salts of higher fatty acids and epoxidized soybean oil — both form Vitco SA.

Costabilizers were chosen from the compounds containing phenolic and/or epoxy amido groups such as Irganox 1076, Reoplast 392 and Irgawax 280, respectively (supplied by Vitco SA).

Preparation of plasticized PVC samples

A Stephan high-speed mixer was used to mix the PVC powder with the plasticizer, stabilizer and costabilizer. The blends were heated up to 100°C. The resulting compositions were homogenized in a single-screw extruder at temperature 150/155/160°C to the form pellets. The product was extruded into a film 0.5 mm thick.

Irradiation and incubation

The films of plasticized PVC were irradiated at a room temperature with an electron beam in a linear accelerator LAE 13/9 at a dose of 25 kGy and then incubated 120 hours at 50°C to simulate a two-years' storage at ambient temperature (ageing) [16].

Methods

The chemical, biological, mechanical and thermal properties of flexible films, as well as melt flow rate (*MFR*) of PVC compositions were determined:

— before irradiation (denoted "before Ir*"),

— after irradiation (denoted "after Ir*"),

— after irradiation and incubation (denoted "after Ir*In*").

Mechanical and thermal properties

Tensile properties were measured at room temperature with an "Instron 4505" tensile tester at a cross head speed of 500 mm · min^{-1}.

MFR values were determined by using II TR plastometer at 190°C with 5 kg load.

Thermogravimetric analysis was performed using Perkin-Elmer thermobalance.

Extraction test

The samples of PVC compositions were suspended in the water and incubated at 70°C for 48 h. Proportion of material and water was 500 cm^2 (both surface of film, 0.5 mm thickness)/100 mL. The aqueous extracts were tested, according to European Pharmacopoeia, to detect reducing and organic compounds, expressed by the milliliters of 0.01 N $Na_2S_2O_3$ solution used in titration per 20 cm^3 of aqueous extract and by UV absorption at wavelength range of 220—290 mm, respectively.

Spectrophotometric analysis

The structural changes of PVC were studied by FT-IR spectroscopy. Films of 0.1 mm thick were prepared by a casting method from the solutions of PVC compositions in trichloromethane. Absorbance was measured within the wave number range of 1700—1800 cm^{-1} corresponding to the carbonyl groups.

Colour stability

The colour effects can be quantified by using trichromatic colorimeter "Momcolor 100". The whiteness (*WI*) and yellowness indexes (*WY*) were determined. Ceramic plaques white and black were used as a background for transparent films and only relative *WI* and *WY* values are meaningful.

RESULTS AND DISCUSSION

Typical commercial medical grade plasticized PVC compositions contain 35% of DEPH plasticizer 1.5% of Ca/Zn salts and 3.5% of epoxidized soybean oil as stabilizers (this stabilizing system is named "standard stabilizer" in the further text).

Two series of PVC compositions, hardness 78±2 Shore A were prepared

— series I: containing modified plasticizing system (mixture of plasticizers *i.e.* DEPH + TOTM) and standard stabilizer,

— series II: a modified stabilizing system (standard stabilizer and costabilizers) and standard plasticizer.

The modification of basic formulation was done by using of additives which:

— contain aromatic groups and can absorb the excitation energy, acting as traps converting this energy into

other non-reacting forms [4, 17] (*e.g.* high molecular weight plasticizer TOTM) (series I),

— can act as radical and HCl scavengers as well as radiation protectors showing the ability of blocking of double bonds formation [10] (series II with costabilizers).

The amounts of additives were chosen empirically. The selected modified PVC compositions of both series are given in Table 1.

Table 1. Formulation of modified PVC compositions

Series/sample	Type of additives		
Series I, MD-1	Plasticizing system: DEHP/TOTM (18/17), phr		
Costabilizers, phr			
Series I:	Irganox 1076	Reoplast 392	Irgawax 280
MD-2	0.15	—	0.4
MD-3	0.15	3.5	—
MD-4	0.15	3.5	0.8
MD-5	0.15	7.0	0.8

The products of PVC degradation can migrate from radiation sterilized medical devices into body fluids and tissues having contact with them. Therefore the migration index of low molecular substances to aqueous extract was used as a screening test of properties of irradiated PVC compositions.

The effect of irradiation and accelerated ageing on low molecular organic substance concentrations in the aqueous extract is presented (Fig. 1) for selected compositions of both series. The amount of organic substances were measured as UV absorbance at wavelengths 222.8—230 nm. Absorbance after irradiation only increased from about 0.15 to about 0.30 for composition with modified plasticizer system (MD-1) (Fig. 1a) and composition of series II with modified stabilizer system, containing the small amount of costabilizer with phenolic and amido groups (MD-2) (Fig. 1b). A distinct increase in the absorbance was observed for both incubated compositions after irradiation (curves 3). The concentration of organic compounds in this case was higher in composition MD-1 in comparison with the composition of series II — MD-2 (UV absorbance of water extract about 0.46 and 0.35, respectively), but for both these samples higher than that permitted by the medical requirements (UV absorbance max 0.3). The acceptable results, from medical point of view (<0.3), were obtained for the compositions MD-3, MD-4 and MD-5 containing the double bonds blockers acting simultaneously as HCl scavengers (compounds with epoxy and amido groups) and radicals deactivators (compounds with phenolic groups). Figure 1 presents, as an example of proper compositions, the results concerning composition MD-4 (Fig. 1c).

Interestingly, the amount of reducing substances (Fig. 2) leached into water from all irradiated and then aged films of series II (column 3), measured by titration as a volume in mL of 0.01 N $Na_2S_2O_3$/20 mL of water extract,

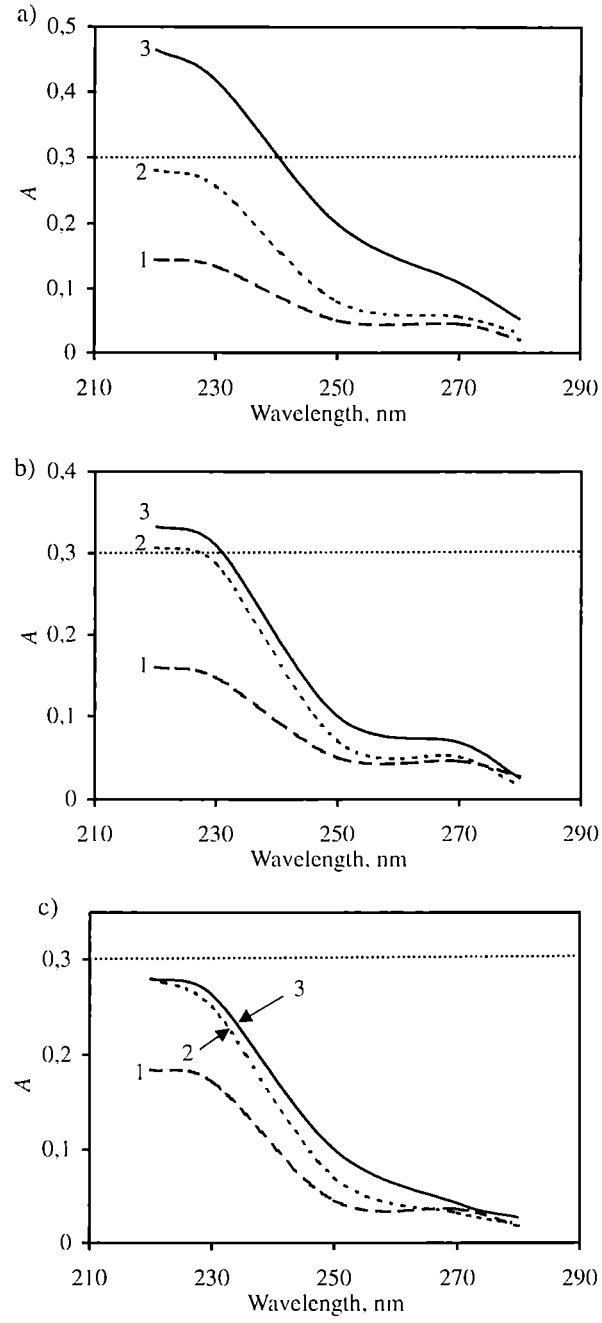

Fig. 1. Absorbance of aqueous extract from PVC compositions: (a) MD-1, (b) MD-2, (c) MD-4; 1 — before Ir, 2— after Ir*, 3 — after Ir*In*, dotted line — maximal acceptable value according European Pharmacopoeia*

is rather low, *e.g.* from 1.5 to 2.4, respectively. These values meet the requirements set for medical materials (max 3.0).

The colour resistance measurements indicate yellowness index of irradiated films, which is a strong function of costabilizers content (Fig. 3). Increasing concentration of blockers of double bonds formation and radicals' scavengers significantly reduced the change in yellowness index of the material after radiation with dose of 25 kGy (sample MD-5).

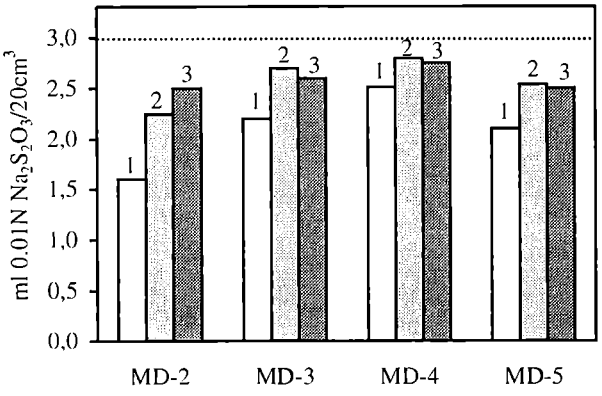

Fig. 2. Effect of ionizing radiation on the content of reducing substances series II (aqueous extract); 1 — before Ir, 2 — after Ir*, 3 — after Ir*In*, dotted line — maximal acceptable value according European Pharmacopoeia*

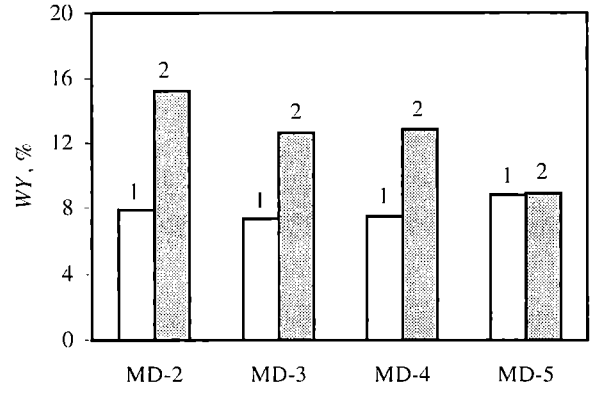

Fig. 3. Effect of ionizing radiation on the colour stability of PVC compositions; 1 — before Ir, 2 — after Ir**

The improvement in thermal and oxidation resistance of irradiated compositions is also observed (Fig. 4). FT-IR spectra of sample MD-3 (Fig. 4a) shows the intensity of carbonyl groups at wavelength of 1700—1800 cm^{-1} slightly increased in the irradiated and then incubated samples (curves 2 and 3, respectively). No oxidation process has been occurred in composition MD-5 having the stabilizer system of highest efficiency (Fig. 4b) — the intensity of carbonyl groups practically did not change after irradiation and accelerated ageing.

The mass loss of only irradiated (not incubated) and than heated up to 250°C compositions amounts about 16% for sample MD-2 (see Fig. 5), and only near 12% in the case of composition MD-5. The irradiation dose of 25 kGy did not effect the tensile and rheological characteristic of all prepared PVC compositions. There are no changes in tensile strength, elongation and melt flow rate for nonirradiated, irradiated and in addition incubated compositions (Table 2). These properties are independent on the compositions of studied samples.

Some chemical and biological properties of the selected PVC compositions (done by the Department of Medical Materials in Drug Institute in Warsaw) are summarized in Tables 3 and 4. The data obtained for irradiated and then

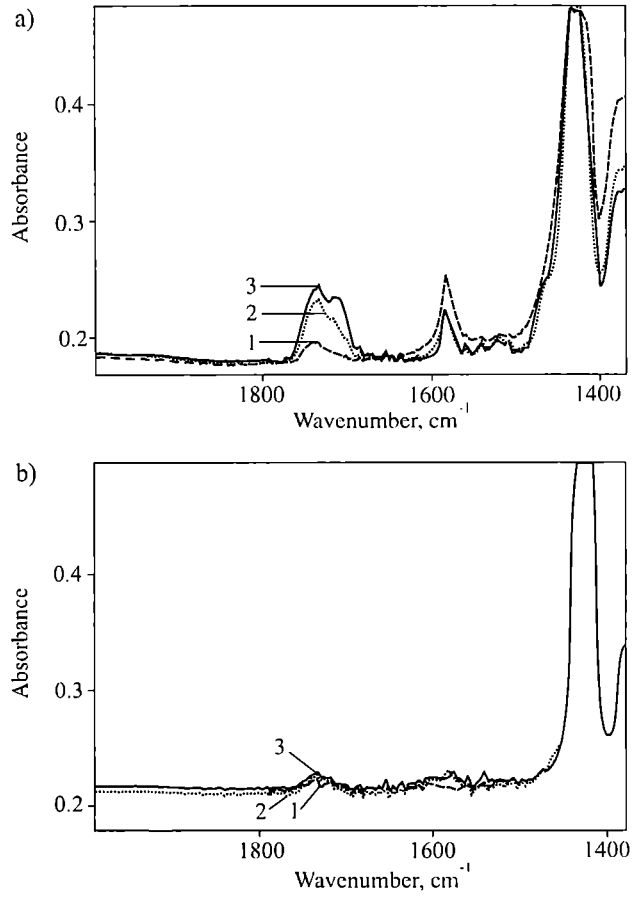

Fig. 4. FT-IR spectra of PVC compositions: (a) MD-3, (b) MD-5; 1— before Ir, 2— after Ir*, 3 — after Ir*In**

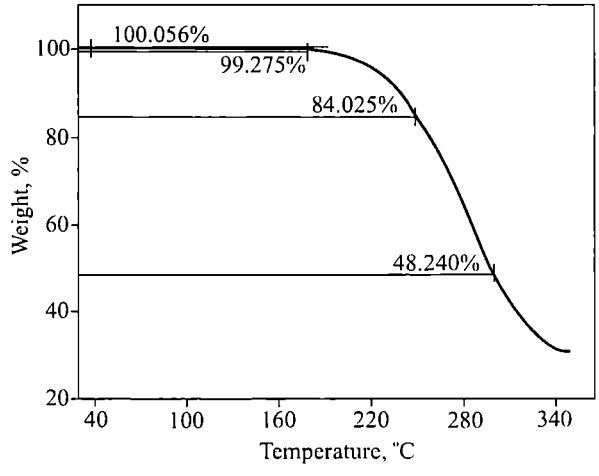

Fig. 5. TGA thermogram of the sample MD-2

incubated films made of PVC composition MD-3 are meeting Pharmacopoeia requirements for medical articles having long-contact with blood. The articles made of this PVC composition can be radiation sterilized with small changes of their physiological properties.

The results indicate that selected additives, improving efficiency of thermal stabilizer, allowed to prepare a plasticized PVC that resisted 25 kGy doses of electron beam radiation and retained colour stability, the biological and

Table 2. Mechanical properties of plasticized PVC compositions

Properties	Before Ir*	After Ir*	After Ir*In*
Elongation stress (100%), MPa	9.6	9.9	9.3
Tensile strength, MPa	19.3	20.0	18.5
Elongation at break, %	330	340	320
MFR g/10 min, 190°C	4.94	4.99	5.0

Table 3. Chemical properties of aqueous extract from PVC composition MD-3

Property	Before Ir*	After Ir*	After Ir*In*
Colour	Such as control sample		
pH (control — 6.26)	6.10	6.02	6.21
Alkalinity, cm^3 of 0.01 N HCl/100 cm^3	0.10	0.15	0.15
Acidity, cm^3 of 0.01 N NaOH/100 cm^3	0.15	0.15	0.15
Pollution with ions			
Reducing substances ml of 0.01 N $Na_2S_2O_3$/20 cm^3	0.65	0.50	0.085
Light absorbing organics, λ=225 nm	0.037	0.108	0.085
Cl^- conc. mg/10 cm^3	as the control sample	as the control sample	as the control sample
NH_4, conc. mg/10 cm^3	as the control sample	as the control sample	as the control sample
Heavy metals (account as Pb^+)	below 1 ppm	below 1 ppm	below 1 ppm
Pollution of heavy metals, ppm:			
Cd	not tested	<0.014	not tested
Ba	not tested	<0.020	not tested
Sn	not tested	<0.620	not tested

Table 4. Biological properties of PVC composition MD-3

Property	Before Ir*	After Ir*
Toxicity and cell toxicity	non toxic	non toxic
Acute toxicity		
Extract in 0.9% NaCl	non toxic	non toxic
Extract in cotton oil, %	non toxic	non toxic
Irritating	non state	non state
Indirect haemolytic activity	as the control sample	as the control sample
Direct haemolysis (requirement <0.3), %	0.11	0.17

chemical properties during accelerated ageing simulating the two-year's long storage at room temperature.

The extent of postirradiation processes such as migration index of low molecular substances, formation of conjugated double bonds change of colour and dehydrochlorination is reduced to acceptable minimum.

CONCLUSIONS

The improvement of radiation resistance of plasticized PVC compositions to the level meeting the fundamental requirements for medical applications (*e.g.* acceptable physiological properties and colour stability) was possible *via* application of the multicomponent synergistic stabilizing system [20].

The results suggest that a properly balanced combination of stabilizer and costabilizers is necessary in order to achieve a radiation stable PVC composition. The developed stabilizing system provides synergistic protection to the PVC and probably plays the combined role: as the thermal processing stabilizer and as the radiation stabilizer as well as a stopper of autocatalytic postirradiation processes occurring in PVC. The accelerated ageing test of postirradiated processes of well stabilized PVC compositions showed that the concentration of low molecular weight organic substances leached into water did not rise with the prolongation of the storage time of the irradiated composition. Also very important is that the mechanical properties and melt viscosity of plasticized PVC samples remained unaffected by the dose of 25 kGy.

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